Drug used in Heart Failure

Objectives:

1- At the end of lectures the students should

2- Describe brifely the pathophysiology of heart failure

3- Identify the causes of heart failure

4- Describe the different classes of drugs used in the treatment of heart failure.

5-Describe the mechanism of the used drugs for treatment of heart failure.

6- Describe the main therapeutic uses , side effects & drug

Red is very very important

Heart failure

Introduction

Heart failiuer = ↓contractility + ↑preload + ↑afterload.

When the heat fails the **compensatory mechanism** will be activated and will produce:

1- **Activate renin-angiotensin-Aldosterone system:**
The sequence of events is :
When the blood volume is low the rennin will be secreted by the liver .. why ?
to transform the angiotensinogen(Ag) to angiotensinogen 1(Ag1), Ag1 will be converted to AgII which is the active from that will cause a vasoconstriction that will lead to increasing in the velocity of the transmission of the blood to the tissues.

2- **Activate sympathetic system:**
To increase the heart rate and the contractility and the conduction velocity of the electrical impulses within the AV node.

The compensatory mechanism may fatigue the heart.

Drugs used in the treatment of heart failure

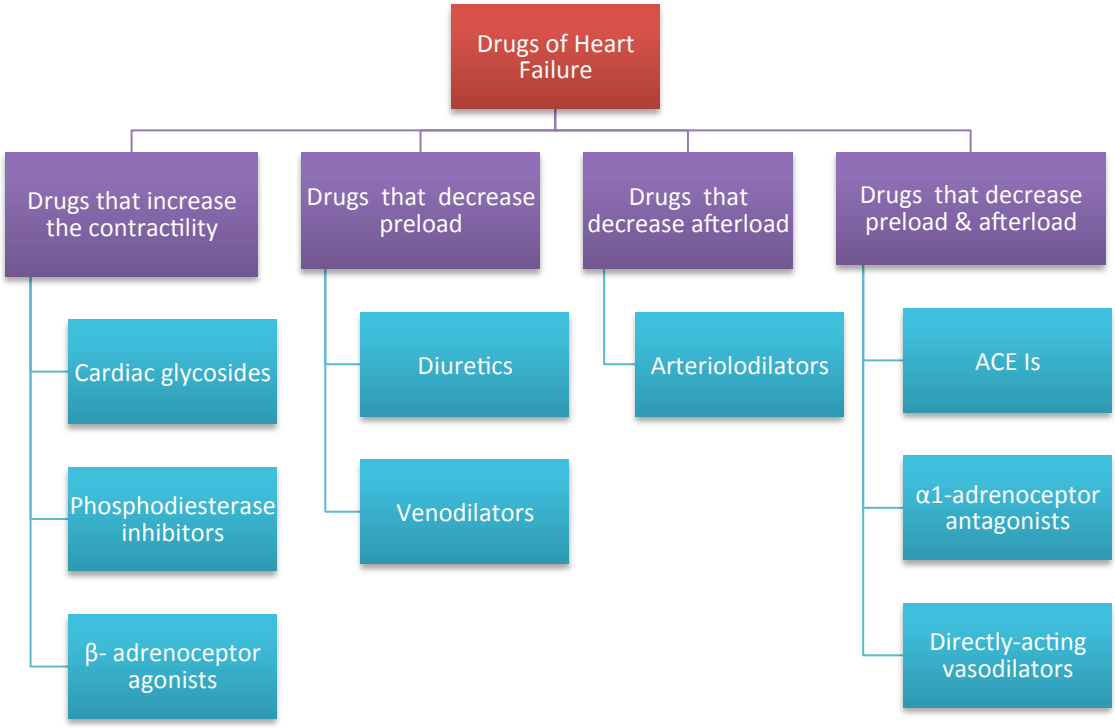
They are 4 groups :

1- **Drugs that increase contractility, drugs that produce + inotropic effect or drugs has cardiostimulatory effect:**
They improve the myocardial contractility.

2- **Drugs that decrease preload:** because the failed heart can't deal with a high volume of blood.

3- **Drugs that decrease afterload:** to decrease the resistance of the aorta.

4- **Drugs that decrease preload & afterload** (they are better than the specialized drugs 2+3).



Drugs that increase contractility

- **Cardiac glycosides**
- **Phosphodiesterase inhibitors**
- **β- adrenoceptor agonists**

Cardiac glycosides

They are 3 drugs : Digoxin is the most commonly used, Digitoxin and Ouabain

In the exam cardiac glycosides means digoxin they are the same.

Drug has narrow therapeutic index.

Drug	PHARMACOLOGICAL ACTIONS	Therapeutic uses	adverse effects	Contraindica-tions	Drug interactions
Cardiac glycosides Or digoxin	1- Increase in force of contraction of the myocardium (+ve inotropic effect) " accompanied by reduction of the size of the failing heart leading to increased cardiac output." .. how ? ▸ By Inhibiting Na^+ / K^+ ATP ase enzyme(Na-K pump), which leads to increase intracellular calcium that will bind with the troponin producing contraction. and the drug may open the ca^{++} channels. 2- As a result from the intracellular increasing in ca^{++}, ca^{++} **will increase the heart excitability and automaticity.** "Adverse Effect" because this it may lead to **arrhythmia(short QT interval when it cause ventricular arrhythmia)** Which is Called: digitalis-induced arrhythmia - digitalis toxicity increases the automaticity of **Purkinji fibers** and they take over as the heart pacemaker **(arrhythmia)** 3- Effects on conduction & refractory period: ► slowing of conduction and prolongation of atrial & A.V. node refractory period. (In ECG : prolongation of the PR interval) ► shortening of ventricular refractory period (In ECG : reduced QT interval) 4- EXTRACARDIAC EFFECTS: #1.explanation - Increase the parasympathetic supply of the heart "vagal activity" leading to : A- Decrease atrial refractory period Leading to conversion of atrial flutter to fibrillation. B- **Slowing of A.V. conduction** C- **Bradycardia (-chronotropic and -dromotropic), so we'll have prolongation of the PR interval.**	1-Chronic congestive heart failure. **2-**Atrialarrhythmias; -Atrial flutter -Atrial fibrillation -Supraventricular tachycardia. **#2 explanation** Because of the parasympathetic effect that will slow the heart rate via the SA node & conduction velocity via AV node.	1- digitalis-induced arrhythmias "can cause any type of arrhythmia especially: - extrasystoles, coupled beats - ventricular tachycardia or fibrillation - A.V.block, cardiac arrest. **2-** GIT: Anorexia is an early sign for the digitalis toxicity. 3- C.N.S: - Headache - visual disturbances - drowsiness.	1- Toxic myocarditis 2- Constrictive pericarditis 3- DC cardioversion	Diuretics→ hypokalemia (arrhythmia) Quinidine : ↑plasma level of digitalis **BY:** displacing digoxin from protein binding site or decreasing the renal execreation. So I have to reduce the dose of digoxin if I'm giving quindine.

#1 Explanation: When the heart has atrial flutter or fibrillation dose all the 300 or 500 go down to the ventricle? NO because there is physiological delay in the AV node ! the AV node may passes 200 impulse to the ventricles from the 300 of the atria , so because it goes to the ventricle it will affect the CO coz if the heart is beating fast means it is not ejecting fully the blood so the CO drops / when I give the digitalis "or even Ca+ channels blockers" then they are just going to the AV node and depressing the conduction there "the digitalis very potent in depressing the AV node because it depress it in two mechanisms (direct and indirect: activation of vagus)" when we slow the conduction in the AV node more than the physiological delay , that's mean u r lowering the number of beats which are transmitted from 200 to about 100 or 120 and this is very significant to the pt, which let the heart sufficient time to eject good amount of blood

#2 explanation: - it induce arrhythmia how we use it in arrhythmia?

because of the ability of digitalis to suppress the conduction thru the AV node by the direct and the increase the vagal activity SO WE ONLY USE IT IN ATRAL FLUTTER to Protect the ventricles from the high impulses of the atria , coz the ventricles is more important so we dont care if the atria will become fibrillated we only focus in the suppressing activity at the AV node whichprotect the ventricles which is more involve in the Cardiac output. (also the contractility increase in the ventricles as it is in the atria because of the digitalis).

Factors That increase digitalis toxicity:

- **Small Lean body mass**
- **Renal diseases** : the drug won't excrete.
- **Hypothyroidism** : the drug won't degrade.
- **Hypokalemia :**
- **Hypomagnesemia** :
- **Hypercalcemia :**

→ increase the activity of the drug on Na^+ / K^+ ATP ase enzyme, so they increase intracellular ca hugely.

Treatment OF ADVERSE EFFECTS:

1- **Stop the digoxin.**
2- **Give diuretic** to increase the rate of execration.
3- **Give Atropine** (muscarinic antagonism) if the patient has AV block, you have to reduce the parasympathetic effect by giving the atropine to prevent cardiac arrest.
4- **Give antiarrhythmics .**
5- **K supplements** to prevent hypokalemia caused by diuretic drugs.

When the patient has **acute digitalis toxicity** the first drug of choice is **FAB fragment** (they are antibodies that will suppress the digoxin).. then go to the other ordinary drugs OF ADVERSE EFFECTS that previously mentioned above.

Drug	Pharmacological Actions	Therapeutic uses
Dopamine	α ,β_1 and dopamine receptors	**Acute L.H.F. mainly in patients with impaired renal blood flow.**
Dobutamine	Selective β_1 agonist **(better to use because it's more selective on β_1)**	**acute heart failure**

β-Adrenoceptor agonists (both given IV)

Why I can not use β-Adrenoceptor agonists in chronic HF ?

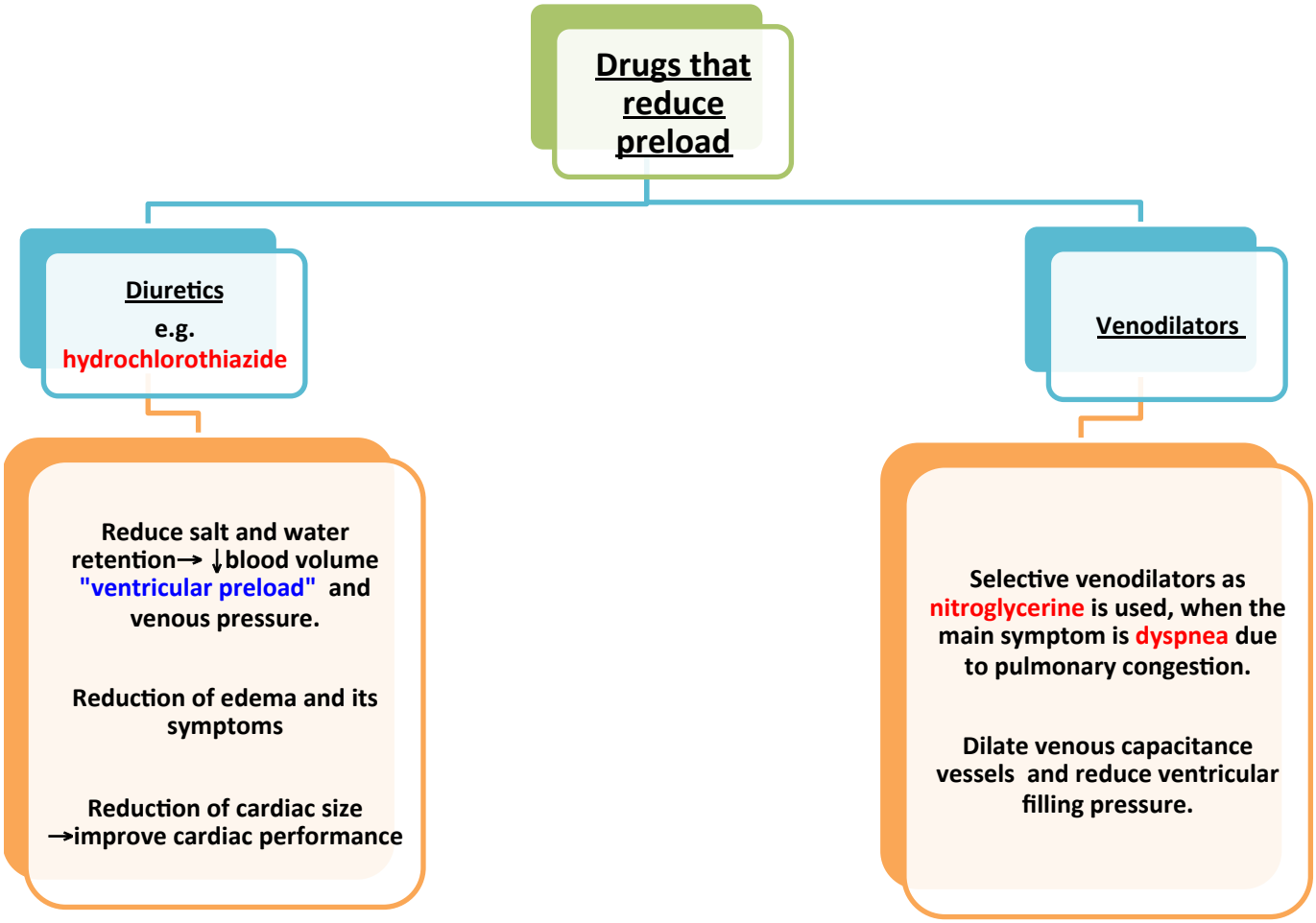
1- they increase heart rate which may lead to angina pectoris.

2- it has tachyphylaxis "Tolerance"

Phosphodiesterase Inhibitors(both given IV)

Bipyridines: (Amrinone , Milrinone (**this one is safer**))

rug	Pharmacological Actions	Therapeutic uses	Adverse Effects
ipyridines	**Inhibit phosphodiesterase isozyme 3 (enzyme that breaks cAMP). By inhibiting this enzyme, cAMP increases & that will increase the ca^{++} influx causing Increased myocardial contraction.** **In the peripheral vasculature : Dilatation of arteries & veins, so will decrease afterload and preload.**	**acute H.F ONLY !!**	**- Nausea ,vomiting** **- Arrhythmias (less than digitalis)** **- Thrombocytopenia "bone marrow depression"** **Liver toxicity** **-** Milrinone **has less hepatotoxic and less bone marrow depression than** Amrinone**.**

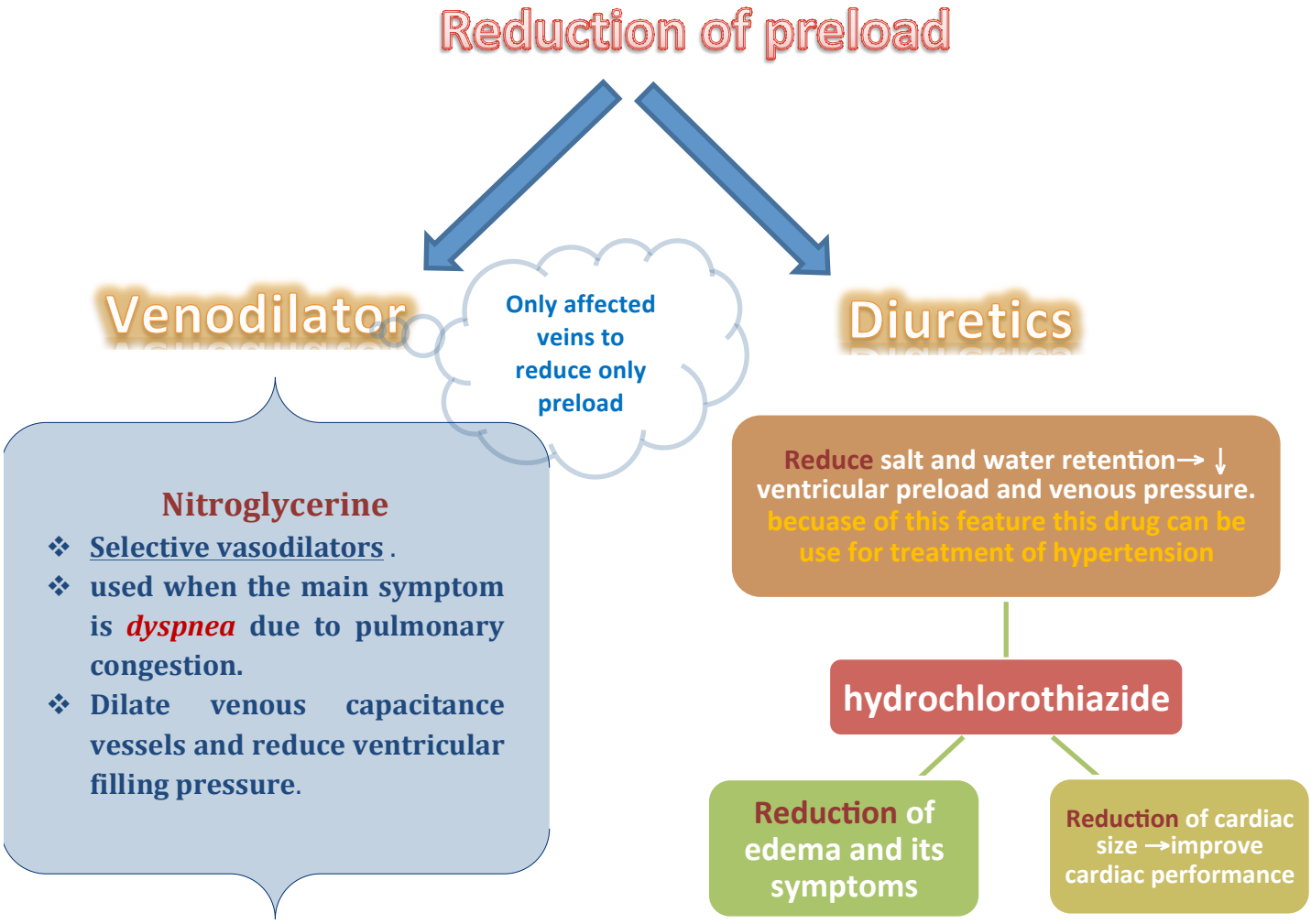


Drugs that reduce afterload (Arteriodilators)

Selective arteriodilators as **hydralazine** is usedwhen the main symptom is **rapid fatigue** due to **low cardiac output**.

Reduce peripheral vascular resistance

Same idea as previous smart art



Reduction of afterload & preload

Direct acting vasodilators

eg: ***Sodium nitroprusside***

given I.V. in refractory heart failure.

Acts immediately and effects lasts for **1-5 minutes.**

Used in emergency, because of its rapid onset of action

Angiotensin converting enzyme (ACE) inhibitors:

MOA:

Inhibit the **SYNTHESIS** of Angiotensin II

Activation of bradykinin system ---> vasodilatation ---> reduce preload and afterload

Angiotensin receptor blockers (ARBs):

MOA:

block AT_1 receptors ---> decrease **ACTIONS (FUNCTION)** of angiotensin II

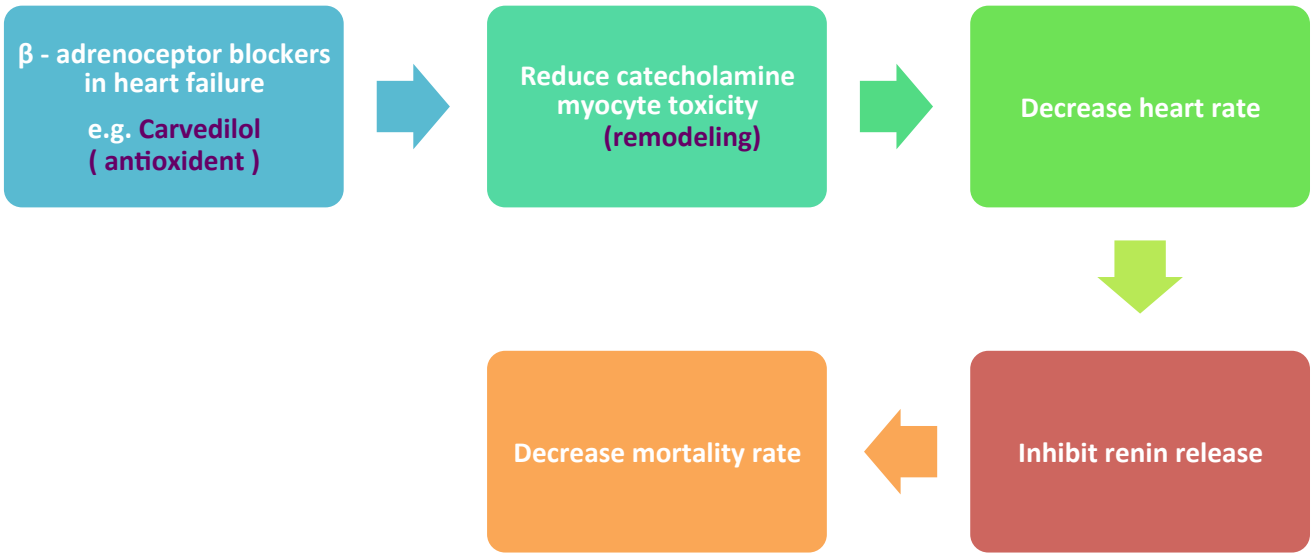
Angiotensin II causes:

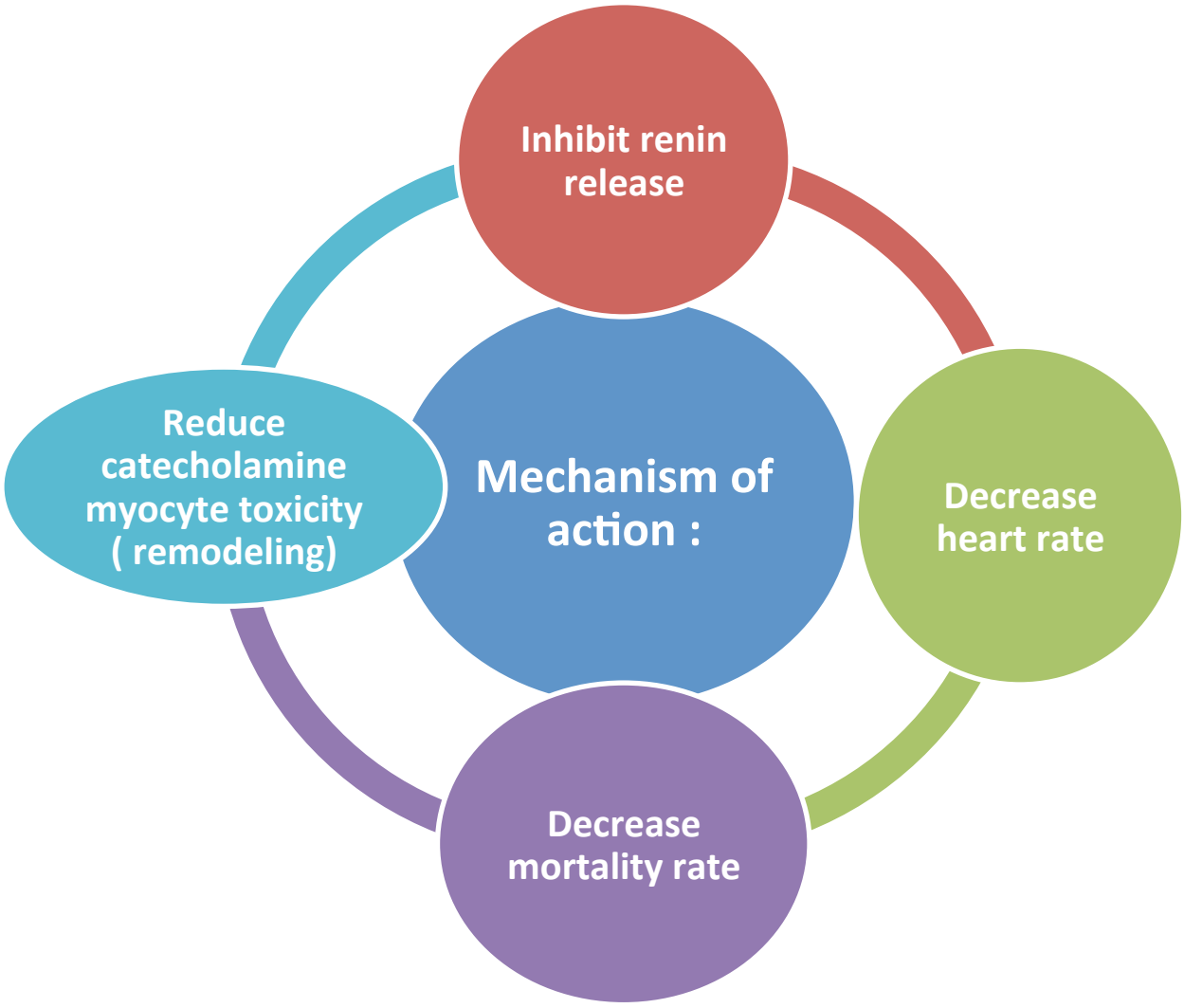
VASOCONSTRICTION – VASOPRESSIN – SYMPATHETIC - ALDOSTERONE

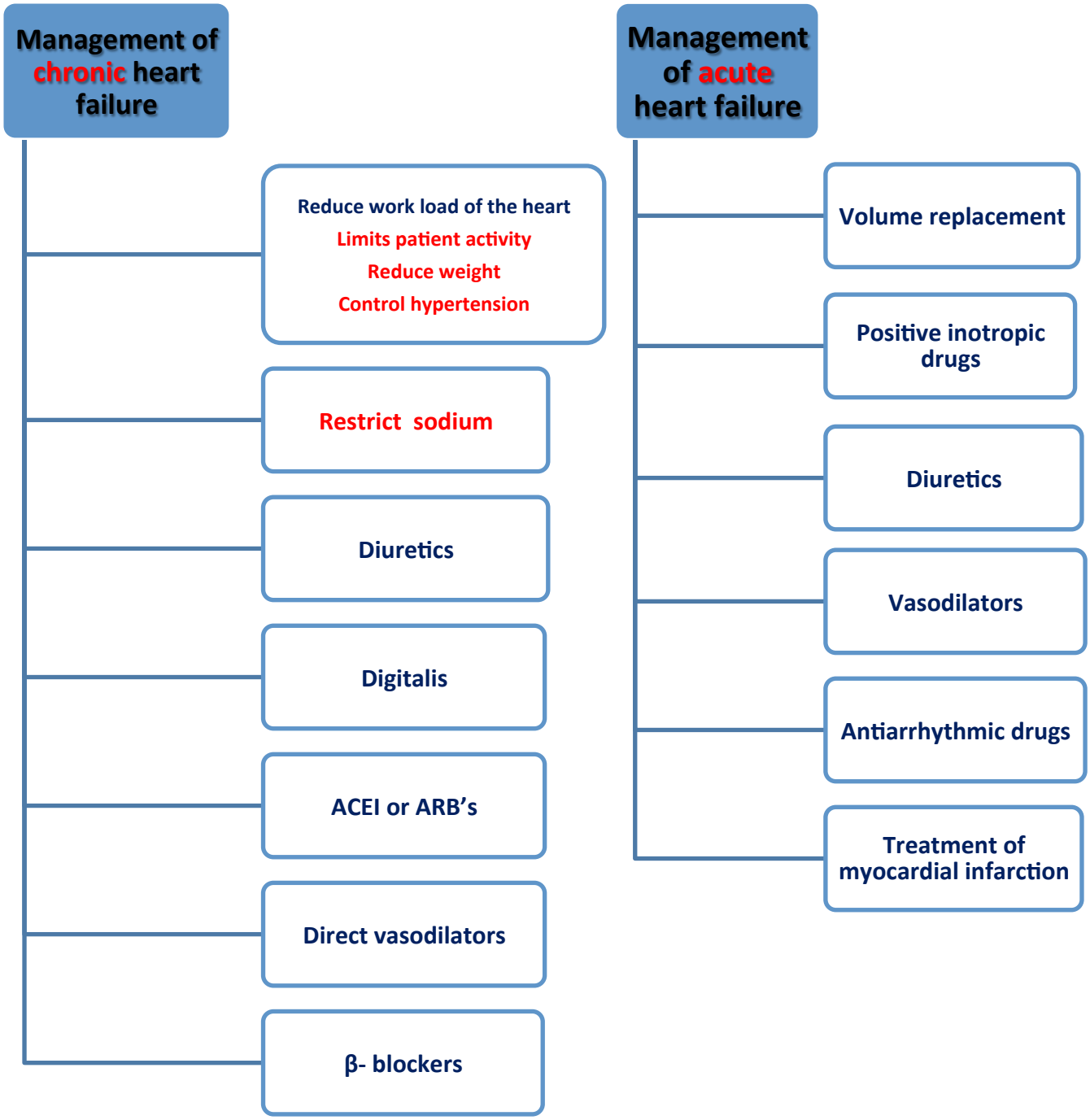
Uses of angiotensin converting enzyme inhibitors & angiotensin receptor blockers in heart failure

↓Peripheral resistance (Afterload)	↓Venous return (Preload)	↓ sympathetic activity	↓ remodeling → ↓ mortality rate

The potency of the Angiotensin receptor blockers is better than ACE inhibitors, because there are other enzymes which will continue to synthesize angiotensin II other than ACE


β - adrenoceptor blockers in heart failure
e.g. Carvedilol (antioxident)
Reduce catecholamine myocyte toxicity (remodeling)
Decrease heart rate
Inhibit renin release
Decrease mortality rate


Inhibit renin release
Decrease heart rate
Decrease mortality rate
Reduce catecholamine myocyte toxicity (remodeling)
Mechanism of action :


Management of chronic heart failure
Reduce work load of the heart
Limits patient activity
Reduce weight
Control hypertension
Restrict sodium
Diuretics
Digitalis
ACEI or ARB's
Direct vasodilators
β- blockers
Management of acute heart failure
Volume replacement
Positive inotropic drugs
Diuretics
Vasodilators
Antiarrhythmic drugs
Treatment of myocardial infarction

Questions

1- Patient admitted to the emergency with acute digitalis toxicity.. what is the first drug of choice :

a) Quinidine
b) Diuretic
c) Atropine
d) FAB fragment

2- 45 years old Patient admitted to the hospital with acute heart failure and it's written in the patient history that the patient suffer from renal failure.. as a doctor which drug you will choose :

a) Dobutamine
b) Bipyridines
c) Digoxin
d) Dopamine

3- Drugs most commonly used in chronic heart failure are:

a) Cardiac glycosides
b) Diuretics
c) ACE inhibitors
d) All of the above

Answers: “hidden”